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(54) Titre: STENT METALLIQUE BIOCOMPATIBLE A REVETEMENT D'HYDROXYMETHACRYLATE

(57) Abstract

The invention provides a hemo-compatible, restenosis-inhibiting metallic stent, comprising a coating of a poly-hydroxy methacrylate derivate selected from the group consisting of poly-hydroxyethylmethacrylate (PHEMA), poly (hydroxyethoxyethyl methacrylate) (PHEEMA), poly (hydroxydiethoxyethyl methacrylate) (PHDEEMA), poly (methoxyethyl methacrylate) (PMEMA), poly (methoxyethoxyethyl methacrylate) PMEEMA, poly (methoxydiethoxyethyl methacrylate) (PMDEEMA), poly (ethylene glycol dimethacrylate) (PEGDMA), and mixtures thereof.

(57) Abrégé

L'invention concerne un stent métallique hémocompatible, inhibant la resténose, comprenant un revêtement de polyhydroxyméthacrylate sélectionné dans le groupe comprenant le polyhydroxyéthyl méthacrylate (PHEMA), le poly(hydroxyéthoxyéthyl méthycrylate) (PHEEMA), le poly(hydroxydiéthoxyéthyl méthacrylate) (PHDEEMA), le poly(méthoxyéthyl méthacrylate) (PMEMA), le poly(méthoxyéthoxyéthyl méthacrylate) (PMEEMA), le poly(méthoxydiéthoxyéthyl méthacrylate) (PMDEEMA), le poly(éthylèneglycol diméthacrylate) (PEGDMA), ainsi que des mélanges de ces composés.

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BIOCOMPATIBLE METALLIC STENTS WITH HYDROXY METHACRYLATE COATING

Technical Field

The present invention relates to the application of a coating of a poly-hydroxymethacrylate derivative to improve the biocompatibility of metal stents intended for implantation or insertion. More specifically, the present invention relates to the coating of metallic stents with effective amounts of a coating of a poly-hydroxymethacrylate derivative which will drastically increase the thromboresistance of the stent, as well as prevent any significant deposit of protein, or the occurrence of mineral encrustation, and thereby achieve inhibition of restenosis.

Background Art

Advances in medical and surgical technology involving the introduction of implantation of foreign materials, such as stents, catheters, prostheses, etc. into body-tissue make the search for the development of materials that exhibit a long-term biocompatibililty more pressing than ever before. A wide range of materials and polymers have been tested and used in medical device applications. These include polyethylene, polypropylene, polyvinylchloride, polyesters, polystyrene, polyurethane, silicone, polysulphone, polyamide, polytetrafluoroethylene, cellulose and its derivatives. Although they have excellent mechanical and physical properties, they were originally developed for the use in industrial manufacturing and not specifically for the biomedical field.

Foremost among the difficulties that need to be addressed within a medical or surgical context are the problems concerning the development of thromboresistant materials and coatings that will resist protein deposits and adverse vessel-wall reactions. Indeed, it is by now well-documented that adverse reactions between foreign or prosthetic surface and blood components, e.g. platelet-activation and thrombogenesis, constitute the single most important factor limiting the use of certain biomaterials. To prevent uncontrolled hemostasis, patients need to be

Another approach is based on a discovery made by Chapman in the late 1970's [See e.g., Chapman, D., et al.: Biomembranes as models for polymer surfaces. *Biomaterials*. Vol. 7, July 1986, pp. 121-5, 126-31 and 252-8; Durrani, AA, Hayward, JA and Chapman, D : Biomembranes as models for polymer surfaces II; The syntheses of reactive species for covalent coupling of phophorylcholine to polymer surfaces. *Biomaterials*, 7:2, 1986 Mar, pp. 121-5; Hall, B., et al.: Biomembranes as models for polymer surfaces. *Biomaterials*. Vol. 10, May 1989, p.219-224; and Hayward, JA, et al.: Biomembranes as models for polymer surfaces IV; ESCA analyses of a phosphorylcholine surface covalently bound to hydroxylated substrates. *Biomaterial*, 7:4, 1986 Jul. pp. 252-8], who observed that intact biological membranes are highly successful in preventing inappropriate blood clotting reactions. He went on to show that the phosphorylcholine head group is essential in imparting biocompatability to the phospholipids in the cell-membrane. Some of the most promising and successful attempts of designing biocompatible coatings to date, try to harness these properties: by covalently binding a phosphorylcholine-group to a metal or polymer they attempt to mimic the external surface of biomembranes.

Disclosure of the Invention

The present invention is based on a different approach. Instead of coating the stent with polyurethane or any of the other polymers cited above, according to the present invention, a coating of a poly-hydroxy methacrylate derivative is applied to a metallic stent which results in a highly biocompatible and thromboresistant coating for said stents.

More particularly, according to the present invention there is now provided a hemo-compatible, restenosis-inhibiting metallic stent, comprising a coating of a poly-hydroxy methacrylate derivative.

The term poly-hydroxy methacrylate derivative, as used herein, is intended to nclude hydroxy, alkoxy, and dihydroxy, i.e. glycol derivatives.

The present invention also provides a process for producing hemo-compatible bioactive restenosis inhibiting metallic stents, comprising the steps of:

a) coating a metallic stent with a liquid which contains poly-hydroxyethylmethacrylate in liquid form;

b) cleaning the stent to extract any remaining residues; and

c) drying the same.

Summary of the invention

Unlike the approach pioneered by Chapman (Ibid), the present invention does not aim at mimicking the cell-membrane directly. Rather, the aimed-for biocompatibility is achieved by applying a coating of a poly-hydroxymethacrylate to the metallic surface of a stent. Current uses of 2-hydroxyethyl-methacrylate (hereinafter referred to as HEMA) or its polymer (hereinafter referred to as PHEMA) include adhesives, artificial nails, lacquers, cosmetic compositions, UV-inks and soft lens applications. Surfaces of plastic devices are modified with PHEMA. Furthermore, it is also used as an anti-adhesive to prevent cell attachment in cell cultures, and as an inducer of trabecular bone in dental implants. As such, its non-toxicity and usefulness in medical and biological applications is well-documented.

According to the present invention poly-HEMA is used as a biocompatigenic coating for metal stents. This PHEMA coating renders the stents biocompatible by covering the metallic surface with a uniformly distributed layer of strongly polar and hence hydrophilic groups. As stated hereinbefore, in addition to PHEMA, there are other acrylic-type polymers which are poly-hydroxymethacrylate derivatives and which are similar in general structure to PHEMA:

Among these derivatives are poly (hydroxyethoxyethyl methacrylate) (PHEEMA), poly (hydroxydiethoxyethyl methacrylate) (PHDEEMA), poly (methoxyethyl methacrylate) (PMEMA), poly (methoxyethoxyethyl methacrylate) PMEEMA, poly (methoxydiethoxyethyl methacrylate) (PMDEEMA), and poly

Alternatively, it may be the case that polar PHEMA coating attracts the polar moiety on circulating phospholipids which then precipitate under the form of a lipid bilayer. In this instance, biocompatibility would again be a consequence of mimicking the thromboresistance of cell-membranes. If this latter hypothesis turns out to be correct, it underscores the possibility of self-assembly and hence self-repair of the very factor that induces biocompatibility. This is an extremely desirable property for a stent, especially in locations where there are considerable shear forces due to strong blood-circulation, such as heart and main arteries. In addition, PHEMA coated stents prevent adverse cell reaction of the injured site, cell growth, and restenosis.

Whatever the explanation, it has now been found that coating of the metallic surface of stents with PHEMA results in the creation of a stable and highly biocompatible coating which makes the stent thromboresistant and prevents the deposition of protein and adverse vessel-wall reactions, thus vastly increasing their value in surgical procedures.

Thus, the present invention enables the prevention or minimization of restenosis that is evident in some cases with the introduction of metallic stents, by providing hemo-compatible bioactive restenosis-inhibiting metallic stents.

2-Hydroxyethyl methacrylate (HEMA) can be polymerized into poly-HEMA (PHEMA), which is a polymer exhibiting a strongly polar character. PHEMA shows minimal bacterial or cell binding but excellent cell biocompatibility, no protein deposition and no blood clotting. This means that blood plaques which might trigger the development of a potentially fatal thrombus will not be formed. As there is little or no bacterial adhesion, the risk of infections is minimized. PHEMA is a coating which can be used on metal based stents, and which makes these stents biocompatible. The stents can be made of stainless steel, Ti-based alloys, shape memory alloys or any other metal, eventually in combination with synthetic or biological materials. The stents are coated with the hydrophilic HEMA-monomer, which is then polymerized by using dielectric heating, UV light, electron-beam

controlled temperature chamber. The heating provides sufficient free radical activity to overcome the effect of the inhibitor, resulting in polymerization of the coating. The heating step is, e.g. about 1.5 minutes in duration in a dielectric furnace when the upper electrode is positioned about 5 mm above the stent. In order to remove any remaining HEMA monomer and/or traces of the inhibitor after the polymerization step, the stent is boiled in water for about 2 to 3 minutes after cooling down. This procedure will leach out any remaining HEMA monomer and/or inhibitor. After boiling, the stents can be dried at a slightly higher temperature. 2-hydroxyethyl methacrylate can be applied directly to the stent or with the help of a primer such as silanes.

In order to further improve the biocompatibility, the surface modification by selective alkaline hydrolysis was studied. It was found that the thickness of the modified layer can be influenced by the reaction temperature, NaOH concentrations and reaction time.

Using at least 30% NaOH, short reaction times and temperatures of at least 90° C, coatings with carboxylic groups in the surface layer were prepared. This method can be used for obtaining hydrophilic medical coatings with further improved properties and further increased biocompatibility.

The scope of the invention includes the coating with a poly-hydroxymethacrylate derivative of all metallic surfaces of stents of all types, as well for only metallic stents and for the coating of stents formed from the combination of metal with synthetic or biologic tissues.

Description of Preferred Embodiments

While the invention will now be described in connection with certain preferred embodiments in the following examples so that aspects thereof may be more fully understood and appreciated, it is not intended to limit the invention to these particular embodiments. On the contrary, it is intended to cover all alternatives, modifications and equivalents as may be included within the scope of the invention as defined by the appended claims. Thus, the following examples which include preferred embodiments will serve to illustrate the practice of this invention, it being understood that the

12. The stents were moved to a UV light chamber and radiated for an additional 10 min. The stents were then placed in the chamber in a way that all sides of the stent were no more than 3 cm away from each lamp.

13. In order to remove any remaining HEMA monomer and/or traces of the inhibitor after the polymerization step, the stent was boiled in water for about 2 to 3 minutes after cooling down.

14. After boiling, the stents were dried at a slightly higher temperature.

15. The stents were then placed on an angioplasty balloon and were inflated to 85% of their range.

16. The stents were weighed and examined under a scanning microscope to determine the uniformity of the coat and its attachment to the stent surface.

17. The stents' surface appeared to be completely covered and to a sufficient level of uniformity. Coating adhesion remained intact even under severe stress.

Example 2

1. A stock solution was prepared by dissolving 120 mg poly-hydroxyethyl methacrylate (PHEMA) IN 1 ML 95% ethanol. It is preferable to use the PHEMA in an as pure as possible form, typically better than 98.4%.

2. The dissolving process was helped by heating the solution to 75 °C and shaking the solution for 1 hr.

3. A separation of undissolved material was reached by centrifuging at 3.g. 2500 rpm for 30 min.

4. The Palmaz-Schatz stent and a Wiktor stent were used in this particular example. Other stents have been used in other tests.

5. The stents were thoroughly cleaned using laboratory detergents and washed in warm water.

6. The stents were left to air dry in a sterile environment (sterile lamina flow hood).

7. The stents were then wetted with the solution by dipping them in the solution to the point where their entire surface was submerged in the liquid.

Claims

5. The process of claim 3 comprising the additional step of adding a cross linking agent.

6. The process of claim 5, wherein said cross linking agent is present in an amount of about 0.1% to 6% weight relative to the weight of the 2-hydroxyethyl-methacrylate monomer.

7. The process of claim 3 wherein the stent is first treated with a primer.

8. The process of claim 3 wherein the stent is made from a metal in combination with a polymer.

9. The process of claim 3 wherein the stent is made from stainless steel.

10. The process of claim 3 wherein the stent is made from a Ti-based alloy.

11. The process of claim 3 wherein the stent is made from a shape memory alloy.

12. The process of claim 3 wherein the polymerization is carried out at atmospheric pressure.

13. The process of claim 3 wherein the polymerization is carried out by dielectric heating.

14. The process of claim 3 wherein the polymerization is carried out by induction heating.

15. The process of claim 3 wherein the polymerization is initiated by at least one of photopolymerization, ionic-polymerization, and chemical-polymerization.

16. The process of claim 3 wherein the polymerization is carried out at elevated pressures.

17. The process of claim 3 wherein the polymerization is carried out at temperatures in the range of 150°C to 230°C.

18. The process of claim 5, wherein said cross linking agent is methacrylic diester of ethyleneglycol.

INTERNATIONAL SEARCH REPORT

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PCT/IL 99/00376

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61L31/10

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61L

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CA 2 226 129 A (HUELS CHEMISCHE WERKE AG) 3 July 1998 (1998-07-03) page 15, line 19 -page 16, line 14 page 20, line 23 -page 21, line 3 ---	1-12,15, 20,21,26
X	WO 96 25897 A (MENLO CARE INC) 29 August 1996 (1996-08-29) claims 1,4,6,14 ---	1-12,15, 20,21,26
A	EP 0 574 880 A (UNITED STATES SURGICAL CORP) 22 December 1993 (1993-12-22) page 4, line 46 - line 55 example 4 -----	1-3,5,6, 15, 18-21,26

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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SCIMED LIFE SYSTEMS, INC. [/]; (). YANG, Dachuan [/]; (). WANG, Lixiao [/]; (). ANDERSON, William, E., II; ().

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(54) Title: DRUG DELIVERY DEVICE FOR STENT

(54) Titre: SYSTEME D'ADMINISTRATION DE MEDICAMENTS POUR STENT

(57) Abstract

A device adapted for mounting on a stent, the device comprising a sheath being made of polymeric material that includes drugs such as pharmaceutical agent(s) or radioactive agent(s) for delivery to an implant site. The sheath includes a main body of a generally tubular shape, and may include mounting means for attaching same to the stent. The device may have a slit therein, and may comprise a helical coil, a cylinder or any other suitable shape or design which fits a particular stent. The sheath may include a coating or coatings thereon containing drugs, surgical adhesives or a combination thereof.

(57) Abrégé

L'invention concerne un dispositif conçu pour être monté sur un stent. Ce dispositif comprend une gaine en matériau polymère contenant des médicaments, par exemple un ou plusieurs agent(s) pharmaceutiques, devant être administrés sur le site d'implantation. Cette gaine comprend un élément principal de forme sensiblement tubulaire et peut comprendre des moyens de fixation permettant de la fixer sur le stent. Le dispositif peut comprendre un fente ainsi qu'un enroulement hélicoïdal, un cylindre ou toute autre forme ou structure adaptée à un stent particulier. La gaine peut en outre comprendre une ou plusieurs couches de revêtement contenant des médicaments, des adhésifs chirurgicaux ou une combinaison des deux.